Briefing Document

Meeting of the Nonprescription Drugs Advisory Committee

September 3, 2014

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SUBMITTED BY

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Executive Summary

On July 29, 2014, the Food and Drug Administration (FDA) announced a meeting of the Nonprescription Drugs Advisory Committee to discuss use of over-the-counter Healthcare Antiseptic Products.[1] According to FDA's announcement, "The committee will discuss the standards used to demonstrate that over-the-counter (OTC) topical antiseptics used in healthcare settings are generally recognized as safe and effective [GRAS/E]. The discussion will focus on antiseptic active ingredients marketed under the OTC Drug Review (also known as the OTC Drug Monograph) for the following healthcare antiseptic uses: healthcare personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative and preinjection skin preparations."

The American Cleaning Institute (ACI)[2] and the Personal Care Products Council (the Council)[3] are pleased to provide this briefing package in response to the FDA's Notice.

The following are the key conclusions presented in this briefing document:

1. The active ingredients used in healthcare antiseptic drug products have a very favorable benefit/risk ratio demonstrated over many years of extensive use. These products clearly save lives by reducing bacterial transmission which can cause infections in healthcare settings. By reducing Healthcare-associated Infections (HAI) (e.g., nosocomial infections), these products also reduce healthcare costs.
2. There is no evidence of adverse health effects in humans.
3. A robust body of research supports the safety of active ingredients used in healthcare antiseptic products. The framework for determining the need for additional safety studies should be based on conventions in the international safety/toxicology community and the significant body of safety data that exists in the public domain.
4. Principles of GRAS/E should be followed in assessing healthcare antiseptic drug active ingredients. FDA should integrate the benefit/risk data, published scientific literature, etc. in reaching a determination of safe and effective.
5. Any suggestion that the benefit or risk of these products is in question, especially by FDA, could lead to unintended adverse consequences if usage patterns were to change in the healthcare setting.

[1] Federal Register Volume 79, Number 145, pp 44042-44043, July 29, 2014.

[2] The American Cleaning Institute (ACI) is the Home of the U.S. Cleaning Products Industry™, representing producers of household, industrial, and institutional cleaning products, their ingredients and finished packaging; oleochemical producers; and chemical distributors to the cleaning product industry.

[3] Founded in 1894, the Personal Care Products Council (the Council) is the national trade association representing the personal care products industry. The Council's membership includes approximately 300 active member companies that manufacture or distribute personal care products, including OTC skin antiseptics. The Council also represents approximately 300 additional associate members who provide goods and services to manufacturers and distributors of personal care products.

We acknowledge FDA for their efforts to finalize the regulatory guidance for healthcare antiseptic drug products. Topical antiseptics have a long and safe history of use in healthcare settings and are a critical component of infection prevention programs worldwide. We feel that the general framework for efficacy determination as established in the previous tentative final monograph[4] and in recent NDA's sets the basis for a final ruling. We feel that the industry and standard setting organizations have a strong and unique perspective of the latest advancements in science and testing methodologies for establishing the efficacy and safety of topical antimicrobials. We look forward to further correspondence and discussions with FDA on this critical topic.

Introduction

The clinical benefit of topical antiseptics in health care settings is well established. In the proposed rule for the consumer antiseptic products, however, the FDA proposes a safety testing program for OTC products similar to those required for new molecular entity (NME) or New Chemical Entity (NCE) review. The active ingredients under the 1994 TFM are not new chemical entities and should not be subjected to requirements that surpass the requirements of a conventional New Drug Application (NDA).

In the FDA's proposal for the consumer TFM, the unsubstantiated justification for additional safety data is stated as "new information regarding the potential risks from systemic absorption and long-term exposure to antiseptic active ingredients" and notes that exposure may be "higher than previously thought."[5] This assertion is not supported by information in the proposed rule for consumer antiseptic products nor in the FDA docket.

The history of the Over-the-Counter (OTC) Drug Review and the OTC Monograph system that it created have shaped the requirements for evidence that demonstrates the safety and effectiveness of OTC monograph drugs. This evidence must prove *general* recognition of safety and effectiveness (GRAS/GRAE), concepts that by their very nature are established by publicly available evidence. The FDA possesses substantial flexibility to implement the GRAS/GRAE standard and make judgments about the adequacy of evidence underlying safety and effectiveness of OTC drugs, including the flexibility to rely on published literature and the proven track-record that comes with substantial human marketing experience. A detailed overview of the OTC Monograph approach and a discussion on how FDA has successfully implemented the general recognition standard is provided in Appendix 1.

FDA is in the process of establishing a GRAS/GRAE framework for consumer and healthcare antiseptic drug products (and has been petitioned to establish a framework for food handler antiseptic drug products) in order to be able to finalize an OTC Monograph for Antiseptic Drug Products. Healthcare antiseptic drug products that fall under the Tentative Final Monograph (TFM) are an established and vital component to infection control programs in U.S. hospital facilities and are necessary to limit the number of Healthcare-associated Infections (HAIs). HAIs are a significant burden to the U.S. healthcare system, from both the perspective

[4] 59 Fed. Reg. 31402, 31406-07, 31433 (June 17, 1994)

[5] 78 Fed. Reg. at 76445, 76454.

of patient outcome and economic consequences. A 2011 survey based on a large sample of U.S. acute care hospitals found that on any given day, about 1 in 25 hospital patients has at least one healthcare-associated infection.[6] There were an estimated 722,000 HAIs in U.S. acute care hospitals in 2011; and about 75,000 hospital patients with HAIs died during their hospitalizations. For perspective, this is more than the number of annual deaths from either breast cancer or colorectal cancer.[7,8] A 2009 report from the U.S. Centers for Disease Control and Prevention (CDC) estimated that the overall annual direct medical costs of HAIs to U.S. hospitals ranges from $28.4 to $45 billion.[9] A recent meta-analysis of costs and financial impact of HAIs on the U.S. Health Care System estimated that the total annual costs for the 5 major sources of infections between 1998 and 2013 are $9.8 billion, with surgical site infections contributing the most to overall costs (33.7% of the total), followed by ventilator-associated pneumonia (31.6%), central line–associated bloodstream infections (18.9%), *Clostridium difficile* infections (15.4%), and catheter-associated urinary tract infections (<1%).[10]

Infection prevention plays a critical role in reducing the overall burden of HAIs and topical antiseptics play a central role in infection prevention programs. In 2009, the CDC estimated that the benefits of infection prevention range from $5.7 to $31 billion.[11] As the burden of antibiotic resistance continues to increase and the number of available treatment options decline, the need for strong infection prevention practices becomes even greater.[12] In 2012, the World Health Organization (WHO) called out infection prevention and control as one of the key domains for targeted antimicrobial resistance containment.[13]

The overall purpose of topical antiseptics is to reduce the level of microorganisms on the skin to help prevent the spread of pathogenic organisms and the occurrence of HAIs. Topical antiseptics in healthcare settings addressed in the 1994 Tentative Final Monograph[14] include the types of products and claims identified in Table 1.

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[6] Magill S, *et al.*, Multistate Point-Prevalence Survey of Health Care–Associated Infections. N Engl J Med. 2014; 370: 1198-208.

[7] American Cancer Society, Breast Cancer Facts & Figures 2013-2014. Atlanta: American Cancer Society, Inc. 2013.

[8] American Cancer Society, Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.

[9] Scott II, RD, The Direct Medical costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf

[10] Zimlichman, E, *et al.*, Health Care–Associated Infections: A Meta-analysis of Costs and Financial Impact on the US Health Care System. JAMA Intern Med. 2013;173(22):2039-2046

[11] Scott II, RD., The Direct Medical costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf

[12] WHO, "ANTIMICROBIAL RESISTANCE: Global Report on Surveillance" 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf

[13] WHO, The Evolving threat of antimicrobial resistance: Options for Action. 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf

[14] 59 Fed. Reg. 31402 (June 17, 1994)

Table 1: 1994 Tentative Final Monograph product types and allowable claims

Product Type	Claim
Healthcare Personnel Handwash / Handrubs	For handwashing to decrease bacteria on the skin
Surgical Hand Scrubs / Rubs	Significantly reduces the number of micro-organisms on the hands and forearms prior to surgery or patient care
Patient Preoperative Skin Preparations	For preparation of the skin prior to surgery. Helps reduce bacteria that potentially can cause skin infection

The majority of currently marketed products are sold under the 1994 over-the-counter tentative final monograph (TFM) for healthcare antiseptic drug products. A limited number are also marketed under the New Drug Application (NDA) process.

The Clinical Benefit & Efficacy of Health Care Antiseptic Drug Products

Critical Points:

1. The clinical benefit provided by topical antiseptics in health care settings is well established and represents the global standard of care.
2. Criteria for determining the efficacy of topical antimicrobial active ingredients (GRAE) and products used in healthcare settings should be based on a framework of both *in vitro* testing and *in vivo* human simulation studies.

Discussion

1. The clinical benefit provided by topical antiseptics in health care settings is well established and represents the global standard of care.

The primary purpose of topical antiseptics in the healthcare environment is to protect patients from exposure to potential pathogens in the environment, on other patients, or on their own body. Healthcare Worker's (HCWs) hands are more likely to be exposed to and colonized by pathogens that cause infections through contact with the environment, wounds, or intact skin of patients (particularly those with risk factors for *Staphylococcus* sp. carriage such as diabetes, dialysis, and chronic dermatitis).[15] HCW hands are contaminated with more pathogens than the hands of the general population due to exposure, dermatitis, length and type of patient care activities; meaning that they are more likely to pick up and transmit pathogens to patients via their hands in the course of their work.[16]

[15] World Health Organization, WHO Guidelines on Hand Hygiene in Health Care. Geneva. 2009.

[16] *Id.*

Topical antiseptics in the healthcare environment were first identified as effective when Ignaz Semmelweis showed in an 1861 publication that puerperal fever was transmitted by physicians who *did not* sanitize their hands between patients.[17]

Healthcare Personnel Handwashes: When hands are visibly soiled, after known or suspected exposure to spore-forming bacteria such as *Clostridium difficile*, or after known or suspected exposure to patients with infectious diarrhea during infectious outbreaks, global recommendations are to wash hands with either non-antimicrobial or antimicrobial soap and water.[18,19] Global organizations such as WHO and CDC and several studies all conclude that topical antiseptic handwashes are more effective than plain soap in removing pathogens from hands in healthcare settings.[20,21,22] Further, a recent meta-analysis found that antimicrobial soap consistently produced statistically significantly greater bacterial reductions than did non-antimicrobial soap.[23]

In addition to these critical roles, use of antiseptic hand washes also provide other significant benefits including a) repeated use of these products has a cumulative effect, as documented by ASTM 1174, and b) can significantly reduce the number of transferred organisms from the hands to a further substrate.[24]

The 2002 CDC guidelines and 2009 WHO hand hygiene guidelines conclude that "antiseptic detergents are usually more efficacious than plain soap and that alcohol based antiseptics are more efficacious than antiseptic detergents".[25]

Maintaining the number of antimicrobial active ingredients used in topical antiseptics provides needed options for alternative products in situations where healthcare personnel

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[17] I.P. Semmelwies, "The Etiology, the Concept and the Prophylaxis of Childbed Fever (1861)," trans. By F.P. Murphy, *Med. Classics* 5. 1941: 350-773.

[18] World Health Organization, WHO Guidelines on Hand Hygiene in Health Care. Geneva. 2009.

[19] Ellingson K, *et al.*, Strategies to Prevent Healthcare-Associated Infections through Hand Hygiene. Infect Control Hosp Epidemiol. 2014 Aug; 35(8):937-60.

[20] Ehrenkranz NJ, Alfonso BC, Failure of bland soap handwash to prevent hand transfer of patient bacteria to urethral catheters. Infection Control and Hospital Epidemiology. 1991, 12:654–662.

[21] McFarland LV, *et al.*, Nosocomial acquisition of Clostridium difficile infection. New England Journal of Medicine. 1989; 320:204–210.

[22] Bottone EJ, Cheng M, Hymes S, Ineffectiveness of handwashing with lotion soap to remove nosocomial bacterial pathogens persisting on fingertips: a major link in their intrahospital spread. Infection Control and Hospital Epidemiology. 2004; 25:262–264.

[23] Montville R, Schaffner DW, A meta-analysis of the published literature on the effectiveness of antimicrobial soaps. J Food Prot. 2011; 74:1875-82.

[24] Boyce JM, *et al.*, "An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products." American journal of infection control 40.8 2012; 742-749.

[25] WHO, The Evolving threat of antimicrobial resistance: Options for Action. 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf

develop irritant or allergic contact dermatitis to a particular antimicrobial agent. Having product and ingredient choices may be important to the healthcare worker with respect to product preference, which then enhances compliance.

Healthcare Personnel Handrubs: Whereas hand washing with soap and water remains a critical pillar of infection prevention in the healthcare environment, global organizations such as the CDC and the WHO now recommend alcohol-based hand rubs (ABHR) for hand hygiene when hands are not visibly soiled.[26,27] These recommendations are supported by the Society for Healthcare Epidemiology of America (SHEA).[28] Among the advantages of ABHR over traditional soap-and-water are: (a) faster microbial kill, (b) higher degree of reduction in microbial load, (c) broader spectrum of microbiocidal activity, (d) relative ease of use and time savings, (e) better skin tolerance in spite of frequent use, (f) convenience and freedom from dependence on sinks and running water, and (e) water conservation.[29] In addition, there is no evidence that bacteria develop resistance to alcohol. These factors, together with evidence for higher levels of compliance with hand hygiene and reduced rates of certain types of hospital-associated infections (HAIs), have promoted wide acceptance of ABHR in healthcare.

Surgical Hand Scrubs / Rubs: Although the requirement for pre-surgical hand antisepsis has never been proven by a randomized, controlled clinical trial there is a large body of indirect evidence supporting its benefit.[30] Current global recommendations for surgical hand antisepsis are to use either a suitable antimicrobial soap or an alcohol-based surgical hand rub.[31]

Patient Preoperative Skin Preparations: The Association of periOperative Registered Nurses (AORN) recommends that preoperative skin antiseptic agents should be used for all preoperative skin preparation.[32] The preoperative skin antiseptic agent should significantly reduce microorganisms on intact skin, contain a nonirritating antimicrobial preparation, be broad spectrum, be fast acting, and have a persistent effect. AORN further recommends that the patient be assessed for allergy or contraindications for the specific antiseptic in skin preparation. Again,

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[26] Boyce JM, Pittet D, Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 2002. 51: 1-45, quiz.

[27] World Health Organization, WHO Guidelines on Hand Hygiene in Health Care. Geneva. 2009.

[28] Ellingson K, *et al.*, Strategies to Prevent Healthcare-Associated Infections through Hand Hygiene. Infect Control Hosp Epidemiol. 2014 Aug; 35(8):937-60.

[29] Boyce JM, Pittet D: Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 2002. 51: 1-45, quiz.

[30] WHO, 2012. The Evolving threat of antimicrobial resistance: Options for Action. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf

[31] *Id.*

[32] Recommended practices for preoperative patient skin antisepsis. In: Perioperative Standards and Recommended Practices. Denver, CO: AORN, Inc. 2013:75-90.

we stress that the availability of options for antimicrobial actives used in topical antiseptics should allow for alternative products to be available. The absence of a broad formulary could put sensitive patients and staff directly at risk.

2. Criteria for determining the efficacy of topical antimicrobial active ingredients (GRAE) and products used in healthcare settings should be based on a framework of both *in vitro* testing and *in vivo* human simulation studies.

a. The framework of *in vitro* and *in vivo* testing set forth in the 1994 Tentative Final Monograph (TFM) remains relevant and has been significantly improved over the last 20 years.

The purpose of topical antimicrobial drug products is to reduce the transmission of pathogenic microorganisms and therefore the risk of infection by reducing the burden of pathogenic organisms on the skin. As such, label statements for these products state that they are used to "decrease bacteria on the skin." Consequently, test methodologies and performance criteria used to assess effectiveness should be consistent with these statements, and ideally would be universally applicable to all active ingredients. We believe that *in vivo* human simulation studies are a valid and feasible way to determine efficacy for topical antimicrobial drug products. Simulation studies have been used in the past to demonstrate the efficacy of antimicrobial products since the publication of the 1978 ANPR.[33] The previous tentative monographs for antiseptics relied on surrogate endpoint measurements to support the efficacy of these products. Similarly, the 1994 TFM required the use of a combination of *in vitro* and *in vivo* testing using standard ASTM methods to demonstrate product efficacy. We agree with FDA's 1994 recommendation for the use of standardized ASTM test methods for *in vivo* confirmation of efficacy of the final formulation and propose to extend that to the GRAE determinations.

Whereas we agree in general with the framework, we propose several improvements based on the latest advancements in standardized, peer reviewed test methods. Some critical points that warrant open FDA discussion include:

i. ASTM has improved ASTM E1174 to address neutralization concerns when evaluating healthcare personnel handwash formulations.

ii. ASTM has developed a standard test method for evaluation of the efficacy of healthcare personnel handrubs (ASTM E2755) to address hand wetness and soil load which can inhibit efficacy.

iii. ASTM has developed a standard test method for *in vitro* time-kill evaluation (ASTM E2783).

iv. ASTM has improved the standard test method for validating product neutralization (ASTM E1054).

[33] 43 Fed. Reg. 64628 (Aug. 4, 1978)

ACI and the Council propose that FDA hold a public feedback session at a date prior to issuance of a new TFM to discuss *in vivo* study design including controls, sample size, efficacy performance criteria and statistical methods.

b. The framework of *in vitro* and *in vivo* testing set forth in the 1994 Tentative Final Monograph is comparable to requirements set forth by global regulatory bodies.

Global regulatory bodies including those in the European Union, Canada, and Australia, recognize surrogate endpoint testing to demonstrate the efficacy of topical antiseptics used in healthcare settings (Table 2). We note that some jurisdictions, including Canada, Brazil, and Australia, allow and/or recommend the same ASTM methods required in the 1994 TFM for establishing efficacy.[34,35,36]

TABLE 2: Comparison of Proposed Coalition Efficacy Requirements and Global Standards[37]

	Efficacy Test	ACI/PCPC Proposal for Healthcare	1994 FDA Healthcare TFM[38]	Health Canada Healthcare Use[39]	Health Canada Institutional Use[39]	Health Canada Antiseptic Monograph[40]	EN 14885 Consumer & Institutional[41]	Australian TGA[42]
Active Ingredient	MIC	Proposed	-	-	-	-	-	-
	Time Kill	Proposed?	-	-	-	-	-	-
	In vivo	Proposed?	-	-	-	-	-	-
	Clinical	-	-	-	-	-	-	-
Final Formulation	MIC	-	Required	-	-	-	-	-
	Time Kill	Proposed	Required	Required	Required	-	Required	Required
	In vivo	Proposed	Required	Required	Required	-	Required	Required

[34] Health Canada. Guidance Document: Human-Use Antiseptic Drugs. Effective November 27, 2009.

[35] Registrations have obtained for topical antimicrobial products through ANVISA (Brazilian National Health Surveillance Agency) using *in vivo* ASTM methods described in the 1994 TFM to demonstrate efficacy.

[36] Registrations have been obtained for topical antimicrobial products through TGA (Australian Therapeutic Goods Administration) using *in vivo* ASTM methods described in the 1994 TFM to demonstrate efficacy.

[37] Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012. JAMA. 2014; 300(4):368-377.

[38] 59 Fed. Reg. at 31432-33, 31445 (proposed 21 C.F.R. § 333.470(a)(2)).

[39] Health Canada. Guidance Document: Human-Use Antiseptic Drugs. Effective November 27, 2009.

[40] Health Canada. Antiseptic Skin Cleansers Monograph. Effective December 11, 2006.

[41] European Standards. EN 14885:2007-01 Chemical Disinfectants and Antiseptics – Application of European Standards for Chemical Disinfectants and Antiseptics.

[42] Registrations have been obtained for topical antimicrobial products through TGA (Australian Therapeutic Goods Administration) using *in vivo* ASTM methods described in the 1994 TFM to demonstrate efficacy.

	Clinical	-	-	-	-	-	-	-

Hyphen (-) indicates testing is not required.

c. The framework of *in vitro* and *in vivo* testing set forth in the 1994 Tentative Final Monograph is consistent with the requirements used currently by FDA to approve NDA healthcare antiseptics.

FDA approval of new drug products for topical antiseptic indications in healthcare settings via the New Drug Application (NDA) route has been based on a combination of *in vitro* studies to assess spectrum of activity and speed of kill, and pivotal efficacy studies based on *in vivo* surrogate end-point trials. Pivotal efficacy studies are based on standard ASTM methods specific for each indication (i.e. ASTM E1173 for patient preoperative preparation; ASTM E1174 for healthcare personnel handwash; and E1115 for surgical hand scrub/rub).

Downing has conducted research into the types of clinical studies used to support NDA approvals from 2005-2012 for antiseptic drugs that do not fall under the Proposed Monograph.[43] Of the NDA approvals that he surveyed, Downing noted that 45% (91/206) of the indications were approved exclusively on the basis of surrogate endpoints. This record demonstrates that FDA has relied successfully on surrogate endpoints to support drug indications. The ASTM *in vivo* test methods closely simulate the use of each type of healthcare antiseptic and allow for a standardized regulatory benchmark to be applied across marketed formulations to support the proposed indication of "[f]or handwashing to decrease the number of bacteria on the skin." Furthermore, FDA has a long history of promoting harmonization among international regulatory authorities with respect to testing requirements, and should adhere to this principle as it develops this monograph.

A review of the Drugs@FDA database indicates that precedent exists for the use of pivotal Phase 3 ASTM surrogate studies to support new drug approvals. Below are just a few examples:

- NDA-21-074: Avagard™ – Surgical Hand Scrub and Heathcare Personnel Handwash Using a Combination of Chlorhexidine Gluconate 1% Solution and Ethyl Alcohol 61% w/w in an Emollient-Rich Lotion Base.[44]
- NDA-20-832: ChloraPrep (Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v)) One-Step (add ref).
- NDA-21-669: Sage Products Inc., 2% Chlorhexidine Gluconate Cloth, Patient Preoperative Skin Preparation.

[43] Downing N *et al.*, Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012, JAMA. 300(4):368-377 (2014).

[44] US FDA. NDA 21-074. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-074_Avagard_medr.pdf.

> The Avagard™ approval, for example, was approved on the basis of two pivotal Phase 3 challenge studies that supported the immediate and persistent reduction in transient microorganisms on the hands (ASTM E1115), plus one pivotal healthcare personnel handwash Study to support the health-care personnel handwash indication (ASTM E1174).[45]

Given the well-established clinical benefit of topical antiseptic products in healthcare settings and the precedence set by FDA for approving novel therapeutics (in particular topical antiseptics), requiring testing beyond surrogate endpoint studies to demonstrate efficacy of topical antiseptic actives and formulated products would be inconsistent and excessive.

The Safety of Health Care Antiseptic Drug Products

The Proposed Rule for OTC consumer antiseptic hand washes represents the FDA's current thinking for establishing Category 1 safety and efficacy standards for active ingredients in antiseptic products applied to the skin (Federal Register, Vol. 78, No. 242, December 17, 2013, p76444). Given the differences in exposure patterns between the general consumer and healthcare professionals, the following discussion focuses on antiseptic active ingredients marketed under the OTC TFM, specifically for the health care setting and for the following uses: healthcare personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative and pre-injection skin preparations.

In the proposed rule for the consumer antiseptic products, the FDA proposes a safety testing program for OTC products similar to those required for new molecular entities ("NMEs") or New Chemical Entity (NCE) review. However, the active ingredients under the 1994 TFM are not new chemical entities and should not be subjected to requirements that surpass the requirements of a conventional NDA. In the FDA's proposal for the consumer TFM, the unsubstantiated justification for additional safety data is stated as "new information regarding the potential risks from systemic absorption and long-term exposure to antiseptic active ingredients" and notes that exposure may be "higher than previously thought."46 However, this assertion is not supported by information in the Proposed Rule nor in the FDA docket.

FDA recognizes the differences in use of health care and consumer antiseptic products when they assert "(w)e believe that these categories are distinct based on the proposed use setting, target population, and the fact that each setting presents a different risk for infection. Therefore, the safety and effectiveness should be evaluated for each intended use separately."

The FDA has not communicated a clear conceptual distinction between assessment of risks and consideration of risk management alternatives for the professional healthcare products. As stated by the National Research Council (NRC 1983) in *Risk Assessment in the Federal Government: Managing the Process* (authorized and signed by former FDA Commissioner Arthur Hull Hays Jr. M.D.), regulatory actions are based on two distinct elements: risk assessment and risk management. Risk assessment is the use of the factual base to define the

[45] The 1994 TFM allowed for simulation studies, including ASTM methods E1174, ASTM E1115, ASTM E1173. 59 Fed. Reg. at 31432-33, 31445 (proposed 21 C.F.R. § 333.470(a)(2)).

[46] 78 Fed. Reg. at 76445, 76454.

health effects of exposure to substances. Risk management is the process of weighing policy alternatives, integrating the results of risk assessment with political concerns to select the appropriate regulatory action.

Risk assessments contain some or all of the following four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. In each step, a number of decision points occur where risk to human health is inferred from the available evidence. Policy decisions determine the extent to which additional data are required to refine the evaluations of hazard and exposure that are combined to characterize risk.

Before declaring that a dataset is inadequate to assess the risks associated with an antiseptic active ingredient, FDA should communicate to the public the margins of safety using all available data to the extent possible. Evaluation of GRAS for OTC Monograph active ingredients should be based on end-to-end safety considerations which take into account the totality of the existing data using an approach that incorporates modern toxicological methods and data interpretation together with post-market analysis. Proposed NDA-type safety standards are unwarranted absent a transparent risk assessment using all available information.

A. Long-term Cohort Studies of Nurses Do Not Signal Adverse Effects

The FDA's proposed evaluation of risks associated with extensive use of antiseptic soaps by healthcare workers should consider the information available in the Nurses' Health Studies (NHS). The NHSs are a series of long-term studies of health outcomes in several large cohorts of nurses.[47] Starting in 1976, the original and the second cohorts (NHS and NHS II, respectively) included approximately 120,000 registered nurses each. By selecting registered nurses for these studies the study authors anticipated that "…because of their nursing education, they would be able to respond with a high degree of accuracy to brief, technically-worded questionnaires and would be motivated to participate in a long term study." Although these studies were initially based exclusively on responses to questionnaires, blood samples (33,000 in 1989-90 and 18,700 samples in 2000-01) were collected "…to identify potential biomarkers, such as hormone levels and genetic markers." Notably, in 1996 and 2004, participants in NHS II were invited to enroll their children (between the ages of 9 and 14) in the Growing Up Today Study (GUTS). GUTS is ongoing and a third cohort of nurses is being assembled to conduct NHS III.

To date, there is no evidence that suggests that use of topical antiseptics leads to adverse health outcomes in nurses. Although these studies were not designed to evaluate risks associated with use of antiseptic soaps, the large size of the cohorts, the long-term follow-up, the inclusion of children in GUTS, and the professional training of the study participants leads to the conclusion that these studies are adequate to detect clinically-relevant health outcomes, including those associated with endocrine effects, that might arise from the use of antiseptic soaps. Thus, the Nurses' Health Studies are a valuable source of real-world information for professional healthcare workers that must be considered by the FDA.

B. MedWatch has Not Identified Safety Concerns

[47] http://www.channing.harvard.edu/nhs/

In considering the risk-benefit of antiseptic active ingredients and the FDA's position that additional safety data are required, FDA should weigh the long record of safety of healthcare antiseptics. FDA closely monitors the safety of drug products through MedWatch, which is an adverse event reporting program that allows stakeholders, students, health professionals (FDA Form 3500), and consumers (FDA Form 3500B) to voluntarily report safety-related problems to FDA. Mandatory reports are required for severe adverse events for medical devices and those that occur during clinical trials (FDA Form 3500A). Initiated in 2000, FDA keeps a comprehensive online database of these complaints.48 A search of this database fails to find safety-related complaints related to antibacterial hand soaps and/or body washes.

In the event that safety issues are detected through the monitoring program, FDA releases "safety alerts," which address the safety concern and make recommendations to minimize risk. The safety alert may include a recommendation to recall the product. To date, no safety alerts have been released in response to concerns related to antiseptic skin products.

C. Hazard Assessment of Actives Should Follow Current Best Practices

The FDA should follow an evaluation and testing strategy that is designed around a weight-of-evidence approach. As one example or model of this approach, the FDA should consider the sequence presented in the Supplement to OECD Test Guideline 404 (OECD 2002).[49]

Based on this sequence of steps, we recommend that the FDA ensure optimal use of the existing hazard and exposure information. The recommended framework is:

1) A public and transparent evaluation of all existing human, animal, and *in vitro* data.
2) Application of Structure Activity Relationship (SAR) models.
3) Consideration of physical-chemical properties of the substances and how these might affect hazard or exposure.
4) Application of *in vitro* or *ex vivo* assays to fill in data gaps as appropriate.
5) Evaluation of the totality of the available studies and, following a weight-of-evidence approach, identification of relevant data gaps that could be filled by conducting animal studies. A relevant data gap refers to a data gap that, were it not to be filled, would have a material impact on the hazard evaluation and, ultimately, the risk assessments for antiseptic active ingredients.

The mode of application, target population, and frequency of use is different in healthcare settings than in consumer use. There is more frequent use by nurses, in some cases rare use by patients (pre-op), and the most relevant concern is tolerability of the formula.

Table 3 below presents a proposed testing framework as a series of steps that allow a weight-of-evidence assessment of safety. In this proposed approach, if no conclusion can be reached at a given step, the next step of the sequence is considered.

[48] MedWatch, The FDA Safety Information and Adverse Event Reporting Program. http://www.fda.gov/Safety/MedWatch/default.htm.

[49] OECD. Test No. 404: Acute Dermal Irritation/Corrosion, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, 2002.

The proposed framework begins with a thorough review of the peer-reviewed literature (Step 1), which is critically important and deserves additional comments. Studies identified during the literature review exercise should not be rejected for inclusion in the hazard identification and assessment phases merely because they were conducted prior to the development and implementation of current testing protocols and quality criteria. We believe that rejecting older studies that were, nonetheless, conducted in accordance with the quality guidelines of their time could exclude important data, some of which might not be otherwise available. The FDA should conduct a Klimisch analysis of the study's reliability, and identify pertinent data that is not currently available from other sources. Moreover, this practice would set a dangerous precedent for the FDA and might endanger the current regulatory approvals of many drugs and medical devices that are critical for the sustained quality of life for millions of individuals and families.

Table 3: Proposed Testing Framework

Proposed Approach by Data Needs	**Approach**	**Value**
Step 1 – Literature review		
An evaluation of existing human, animal and *in vitro* data.	A search is conducted to identify and locate all hazard/toxicity studies. Studies are evaluated to determine applicability to the hazard assessment.	Ensures optimal use of the existing hazard and exposure information. Allows an initial identification of data gaps.
Step 2 – Read across/*in vitro*/*in silico*		
Application of - Read-across - *in vitro* studies - (Q)SAR	Results of testing conducted on structurally related substances should be considered. *In vitro* studies should be evaluated and, as warranted, used in the hazard assessment. Validated and accepted (Q)SAR approaches should be used to identify hazards.	Together, these techniques could help fill in data gaps when human, animal, or *in vitro* data are not available or deemed to be insufficient.
Step 3 – New *in vitro* or *in vivo* assays		
Tolerability - Irritation - Sensitization - The mode of application and frequency of use by healthcare workers suggests that the most relevant concern is tolerability of the	- *in vivo* - In healthcare settings, nurses are expected to be the most intensive users of antibacterial products. Use by patients as part of pre-op is expected to be brief and short term. Thus, the most relevant concern is dermal tolerability (dermal irritation and sensitization) of the formulas. - We propose that the FDA consider the use of final products to assess	Allows identification of doses associated with skin irritation and sensitization.

Proposed Approach by Data Needs	Approach	Value
formula.	tolerability and to use existing data on actives to assess safety of the ingredients.	
In vitro assessment of dermal absorption and metabolism	- *In vitro* - Assume a default conservative absorption rate	Allows bridging of test results obtained from oral studies to the results that could be expected or excluded when the substance is administered dermally.
Step 4 – Data gaps assessment		
Evaluation of the totality of the available studies and, following a weight-of-evidence approach, identification of material data gaps that could be filled by conducting animal studies.	FDA should not discard older studies that were conducted using the standards of quality required by FDA at the time the studies were conducted. When data from an oral study are available, these would be evaluated in conjunction with *in vitro* study results, pharmacokinetic analyses, and, where possible, QSAR analysis, to determine which effects might be expected or excluded when the substance is administered dermally.	This step will allow the FDA to identify relevant data gaps. Relevant data gaps are those that, were they not to be filled, would have a material impact on the hazard evaluation and, ultimately, the risk assessments for antiseptic active ingredients.

D. Evaluate Hazard and Dose-Response from All Available Studies and Authoritative Bodies

In the proposed rule for OTC consumer antiseptic hand washes, FDA identified several potential risks in the context of long-term use of topical antiseptic products (i.e., systemic exposure, hormonal effects, and potential for development of antibacterial resistance) and requested additional animal testing to address these potential hazards.

Consistent with NRC 1983, the FDA should identify all available toxicity studies, conduct a Klimisch[50] analysis of each study's reliability, and identify all pertinent lowest observed adverse effect levels (LOAELs), no observed adverse effect levels (NOAELs), benchmark dose, and dose-response profiles. The FDA's evaluation of these studies ought to be conducted in a collaborative and transparent manner so that the criteria used to accept and reject the study are clear and in keeping with current, accepted practices.

For example, industry comments to the proposed rule for consumer products evaluated the safety database for chloroxylenol and identified a number of studies that the FDA had either

[50] Klimisch H-J, Andreae M and U. Tillmann, A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg. Toxicol. Pharmacol. 1997; 25, 1 – 5.

missed or dismissed, including studies that provide critical hazard and dose response information.[51]

Following the evaluation of the available studies, we urge the FDA to apply modern in vitro and Quantitative Structure Activity Relationship (QSAR) models to address other remaining data gaps or to refine its understanding of the available studies. Pharmacokinetic studies could be used to extend the results of oral toxicity studies to a dermal exposure scenario without the necessity of conducting additional studies.

Only after these approaches are exhausted and remaining critical data gaps are identified, should the FDA consider the need to conduct additional studies in animals. The findings from all the available toxicity/hazard assessment studies would be combined with an assessment of exposure to the antiseptic actives in order to characterize risks.

Other scientific and regulatory bodies have performed risk assessments on antiseptic active ingredients that can support FDA's investigation. The European Commission's Scientific Committee on Consumer Safety (SCCP)[52,53] Health Canada, [54] and Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[55] published comprehensive risk assessments that provide hazard and dose-response assessments for critical safety endpoints, quantify cumulative exposures, and identify margins of safety.

E. Understand Exposure in the Context of Available Animal, *In Vitro*, and Human Data

A robust analysis of current knowledge about human exposure and risk should be the foundation of establishing GRAS status for the active ingredients that have been used for decades; this approach is consistent with the declared intent of the OTC Monograph process.

The FDA has not provided to the public a quantitative assessment of the extent of human or environmental exposure to active ingredients in antiseptic skin products. Key assumptions for human exposure regarding the frequency of application, skin surface area, amount of active ingredients applied to skin, and rates of dermal absorption have not been evaluated in a transparent and public process.

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[51] Exponent, FDA Consumer Antiseptics Rule: FDA Request for Data on Safety and Efficacy of Chloroxylenol. Prepared for American Cleaning Institute. June 12, 2014.

[52] Scientific Committee on Consumer Products (SCCP), Opinion on Triclosan. European Commission Health and Consumer Protection Directorate General SCCP/1192/08. 2008.

[53] Scientific Committee on Consumer Safety (SCCS). Addendum to the SCCP Opinion on Triclosan (SCCP/1192/08) from January 2009. European Commission Health and Consumer Protection Directorate General for Health & Consumers. SCCS/1414/11. 2011.

[54] Health Canada 2012 Preliminary Assessment Report on Triclosan. *Canada Gazette*, Part I: Vol. 146 No. 13 - March 31, 2012.

[55] National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Triclosan, Priority Existing Chemical Assessment Report No. 30. Australia Department of Health and Ageing. 2009.

Before determining that new safety studies are necessary, FDA should assess the magnitude of systemic human exposure and compare it to findings from the available animal, *in vitro*, and human data, to the extent possible, and attempt to bridge data gaps using reasonable conservative assumptions. Understanding the magnitude of human exposures prevents the unnecessary use of laboratory animals and waste of resources to generate toxicology data that will not further inform potential safety decisions.

F. There Is Little Evidence of Higher Systemic Exposure to Active Ingredients

In the proposed Consumer TFM, the FDA indicated that exposure to these products is "higher than previously thought". In a healthcare setting, exposure is limited by established procedures designed to control HAIs. These procedures are required to save the lives of patients. Furthermore, these procedures have been in place for many years, and there is no indication of increased exposure. It is requested that FDA provide evidence to support the statement that a "higher than previously thought" exposure is associated with the use of these ingredients as stated in the proposed Consumer TFM; such evidence does not appear in the public docket for the consumer antiseptic rule and FDA has not made the evidence it has in hand available to stakeholders. To determine that this statement applies in the healthcare setting, including healthcare personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative and pre-injection skin preparations, the FDA should document the level of systemic exposure from antiseptic skin products that was used in its prior safety assessment, and how it differs from new information the agency has received.

FDA should establish definitive case conditions before declaring a situation of higher risk, imminent or otherwise. For example, FDA cites studies for triclosan to support its statement that systemic exposure to topical antiseptic active ingredients may be greater than previously thought.[56,57,58] However, the data in these studies do not suggest an increase in systemic exposure over time. These studies reveal an increase in analytical detection limits, which is not equivalent to, nor should be interpreted as, an increase in exposure. Absorption of triclosan following oral exposure is relatively rapid and complete, with the predominant route of elimination from the body being urine. Approximately 90% of triclosan and its metabolites in the human body would be expected to be eliminated in urine.[59] If individual use and daily intake of triclosan products is assumed to be constant, the samples taken as part of the National Health and Nutrition Examination Survey (NHANES) a steady-state concentration of triclosan in

[56] Calafat, A. M. *et al.,* Urinary Concentrations of Triclosan in the U.S. Population: 2003–2004. Environmental Health Perspectives. (2008); 116: 303–307.

[57] Dayan, A D, Risk Assessment of Triclosan [Irgasan] in Human Breast Milk. Food and Chemical Toxicology. (2007); 45: 125–129.

[58] Centers for Disease Control and Prevention, Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March, 2013.

[59] Rodricks, JV, Swenberg, JA, Borzelleca, JF, Maronpot, RR and Shipp, AM. Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 2010; 40(5): 422–484.

urine.[60] These data do not, however, indicate there is greater systemic dermal exposure. Furthermore, the estimated oral exposures that would represent be associated with these urine concentrations are calculated to have large margins of safety (>1000), suggesting that systemic exposure from ingestion or dermal penetration would have to increase significantly to increase safety concerns.[61] Given the absence of risk, and the very large margins of exposure in this risk assessment, further animal testing to evaluate a purported risk from increased systemic exposure to antiseptic active ingredients is simply not justified.

[60] Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES). Atlanta, GA. http://www.cdc.gov/nchs/nhanes.htm.

[61] Rodricks *et al.* Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 2010; 40(5): 422–484.

G. Animal and Human Pharmacokinetic Data Provide a Measure of Exposure

In the Proposed Consumer Rule, FDA comments that the lack of pharmacokinetic data prevents FDA from calculating a margin of exposure for risk assessment.[62] Although the safety evaluation of drugs may rely on correlating findings from animal toxicity studies to humans based on kinetic information in both species, safety evaluations for antiseptic ingredients in healthcare products are not based on kinetic information under standard international practice. Instead, safety evaluations are based on conservative assumptions of exposure, rates of dermal absorption, and potential differences between species.[63,64,65,66] Kinetic information may be required when use of conservative assumptions fails to provide a sufficient margin of exposure. Using these conservative and internationally accepted approaches, other scientific bodies and regulatory authorities have been able to complete the risk assessment for these types of ingredients in formulations with much greater levels of human exposure.[67,68,69,70]

H. Animal Studies Suggesting Hormonal Effects Are Not Applicable to Human Exposure

In determining the need for additional data or understanding the significance of existing data, it is important for FDA to consider that the endocrine system is complex with significant differences among organisms. Many of the studies cited by FDA as raising concern for hormonal effects from antiseptic skin products are rat thyroid studies.

The thyroid system has been extensively studied for differences among species and genders. For example, there are species differences in the plasma half-lives of thyroid

[62] 78 Fed. Reg. at 76453.

[63]Scientific Committee on Consumer Products (SCCP), Opinion on Triclosan. European Commission Health and Consumer Protection Directorate General SCCP/1192/08. 2008.

[64] Scientific Committee on Consumer Safety (SCCS), Addendum to the SCCP Opinion on Triclosan (SCCP/1192/08) from January 2009. European Commission Health and Consumer Protection Directorate General for Health & Consumers. SCCS/1414/11. 2011.

[65] Health Canada 2012 Preliminary Assessment Report on Triclosan. *Canada Gazette*, Part I: Vol. 146 No. 13 - March 31, 2012.

[66] National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Triclosan, Priority Existing Chemical Assessment Report No. 30. Australia Department of Health and Ageing. 2009.

[67] Scientific Committee on Consumer Products (SCCP), Opinion on Triclosan. European Commission Health and Consumer Protection Directorate General SCCP/1192/08. 2008.

[68] Scientific Committee on Consumer Safety (SCCS), Addendum to the SCCP Opinion on Triclosan (SCCP/1192/08) from January 2009. European Commission Health and Consumer Protection Directorate General for Health & Consumers. SCCS/1414/11. 2011.

[69] Health Canada 2012 Preliminary Assessment Report on Triclosan. *Canada Gazette*, Part I: Vol. 146 No. 13 - March 31, 2012.

[70] National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Triclosan, Priority Existing Chemical Assessment Report No. 30. Australia Department of Health and Ageing. 2009.

hormones.[71] In most mammalian species, the thyroid hormones T3 and T4 are bound to plasma proteins and are, therefore, unavailable for metabolism, serving as a buffer for changes in peripheral T3 and T4 levels. In addition, humans have high affinity T3 and T4 binding globulins and a large percentage of T3 and T4 are bound to these proteins.[72] In contrast, rats and mice lack these binding proteins and only a small fraction of T3 and T4 is bound to proteins. This results in high free (unbound) T3 and T4 available for metabolism, which in turn results in a faster hormone turnover in rodents when compared to humans.[73]

The reported plasma half-lives for T4 are 12-24 hours and 5-9 days in rats and humans, respectively.[74] Therefore, due to the rapid hormonal turnover, the rat thyroid gland would work harder (TSH levels are 6-60 times higher in rats) to maintain T3 and T4 within physiological levels.[75] This will make the thyroid gland in rats more susceptible to chemical perturbation of thyroid hormone homeostasis. Also, the levels of TSH are higher in male rats than in female rats, resulting in higher demand on the thyroid gland.[76] Therefore, chemicals that interfere with thyroid hormone homeostasis would likely have more impact in male rats than female rats.[77] Known differences between human and selected animal models should be considered before relying on animal results for concluding there are potential human safety concerns.

I. FDA Should Take a Flexible Approach on Measuring Hormonal Effects

Evaluation of potential hormonal effects can be addressed by the interpretation of repeat-dose or developmental and reproductive toxicity testing (DART) data. FDA defines a "hormonally active compound" as a "substance that interferes with the production, release, transport, metabolism, binding, activity, or elimination of natural hormones, which results in a deviation from normal homeostasis, development, or reproduction."[78] Results from *in vitro* high throughput screening fail to satisfy this definition. Despite varying modes of action, actual adverse effects from endocrine disrupting chemicals are typically manifested as: (1) alterations in

[71] USEPA. Assessment of thyroid follicular cell tumors. Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

[72] Personal Care Products Council (PCPC) – Cosmetic Ingredient Review (CIR). Final Report on Triclosan. December 14, 2010.

[73] *Id*.

[74] USEPA Assessment of thyroid follicular cell tumors. Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

[75] *Id.*

[76] Chen, HJ, Age and sex difference in serum and pituitary thyrotropin concentrations in the rat: influence by pituitary adenoma. Exper Gerontol. 1984; 19:1-6.

[77] USEPA Assessment of thyroid follicular cell tumors. Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

[78] 78 Fed. Reg. at 76455.

development; (2) reproductive impairment; and/or (3) reduction in growth. These types of effects can be noted in traditional DART studies of antiseptic active ingredients.

Section 2 of the proposed consumer rule states that "data are also needed to assess whether antiseptic active ingredients have hormonal effects that could produce developmental or reproductive toxicity."[79] We agree that toxicological risk assessment should consider whether, under conditions of use, an ingredient could cause adverse effects as a result of its ability to interfere with endocrine homeostasis. The proposed rule also correctly states that general and reproductive toxicology studies are generally adequate to identify potential hormonal effects. We welcome the apparently flexible approach to determining risks to endocrine-sensitive tissues on a case-by-case basis. However, FDA should emphasize that a repeat-dose or reproductive and developmental toxicity study will provide the point of departure for an ingredient that acts by an endocrine mode of action.[80] These animal studies form the highest tier of endocrine testing strategies.[81] Therefore, where data from these studies exist, there is rarely a need to go back and generate *in-vitro* data to inform the risk assessment. As a general principle, therefore, FDA should not require further testing for endocrine modulation, where the adverse outcomes associated with endocrine modes of action have already been adequately addressed in existing *in vivo* tests.

J. FDA Should Reconsider the Requirement for Dermal Carcinogenicity Studies

For the majority of the active ingredients listed in the Proposed Rule for consumer antiseptics, a good quality oral carcinogenicity data set exists, along with *in vitro* genetic toxicology studies. While there are absorption, distribution, metabolism and excretion (ADME) differences between oral and dermal exposure, in the absence of tumors in an oral study, and provided that good quality *in vitro* genetic toxicity data are available, it is difficult to envisage which modes of action would cause concern for these ingredients when applied by the dermal route. Under international standards, "[s]ince carcinogenicity studies are time consuming and resource intensive they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential."[82] Furthermore, "[p]harmaceuticals showing poor systemic exposure from topical routes in humans may not need studies by the oral route to assess the carcinogenic potential to internal organs."[83]

We are not aware of a chemical that provides negative *in vitro* genetic toxicity data and negative oral carcinogenicity data, but is positive by the dermal route. In addition, it is highly unlikely that intermittent dermal exposure would result in systemic exposures higher than those obtained following oral exposure. We therefore strongly advocate that, rather than establishing

[79] *Id.*

[80] (*e.g.*, NOAEL, BMDL10)

[81] *See, e.g.*, EPA, Endocrine Disruptor Screening Program, *available at* http://www.epa.gov/endo/.

[82] International Conference on Harmonization - Safety, Guideline for Industry: The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals, at 1 (March 1996). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074911.pdf.

[83] *Id.*

"studies to be performed," FDA rephrases the proposal to focus on "health effects to be addressed in the safety assessment." This will allow the use of a more integrated and data-based approach to risk assessment.

Where they exist, FDA should use the results of the available oral cancer studies, *in vitro* studies, known exposure conditions and real-world marketing experience to assess the potential for dermal carcinogenicity instead of requiring new dermal cancer studies.

K. There Is No Evidence of Real-World Antimicrobial Resistance from Use of Healthcare Antiseptics

Antimicrobial resistance is an issue demonstrated to occur due to the indiscriminate use of antibiotics, but not to use of antimicrobial hand soaps and/or body washes. Recently, a group of experts participated in a workshop to evaluate the interconnection between microbial resistance to biocides and antibiotics.[84] They found that even though mutant strains resistant to antibiotics have been identified to have transient resistance, the observed level of resistance to biocides was lower than predicted because the concentration required for the expression of resistance was toxic to bacteria. When molecular mechanisms were evaluated in three different scenarios, the conclusion was that biocides show very low correlation coefficients with antibiotic resistance.

While antimicrobial resistance has been demonstrated in laboratory settings, it has not been demonstrated in real world scenarios, as reflected by data from current monitoring programs. Recent studies have reinforced the evidence that resistance and cross-resistance associated with biocides and antiseptics is a laboratory phenomenon, observed only when tests are conducted under conditions that are not clinically relevant.[85]

Studies about the mechanism of antiseptic action are important as a research tool, but would be an unrealistic requirement for a GRAS determination. Identifying cellular targets of antimicrobial activity is not a simple or straightforward undertaking. Data characterizing the potential for transferring a resistance determinant to other bacteria is also an unrealistic requirement for GRAS determination. Currently, it is unclear which methods could be used to determine the transfer of resistance. Furthermore, transfer of resistance by exposure to an antiseptic active is a theoretical risk.

There is little credible evidence that antiseptic hand products play any role in antibiotic resistance in human disease. While some *in vitro* lab studies have been successful in forcing the expression of resistance in some bacteria to antiseptic active ingredients, real world data from community studies using actual product formulations, show no correlation between the use of

[84] Oggioni MR, Furi L, Coelho JR, Maillard J-Y, Martinez JL, Recent advances in the potential interconnection between antimicrobial resistance to biocides and antibiotics. *Expert Rev. Anti Infect. Ther.* 2013; 11(4), 363-366

[85] Condell O, Iversen C, Cooney S, Power KA, Walsh C, Burgess C and Fanning S, Efficacy of Biocides Used in the Modern Food Industry To Control *Salmonella enterica*, and Links between Biocide Tolerance and Resistance to Clinically Relevant Antimicrobial Compounds. *Applied and Environmental Microbiology.* 2012; 78, 3087-3097.

such products and antibiotic resistance.[86,87,88,89,90,91,92,93,94] Further evidence of real world data showing no antimicrobial resistance development after the continued use of consumer products containing antimicrobial active compounds can be extracted from oral care clinical studies. These provide *in vivo* data, under well controlled conditions, on exposure to antimicrobial-containing formulations over prolonged periods of time (e.g., 6 months to 5 years). A considerable number of studies are available in the scientific literature; these have been reviewed by Gilbert *et al.* (2007) and Sreenivasan (2002).[95,96] A recent 5-year study of triclosan-containing products has been reported.[97]

[86] Rutala WA, Weber DJ, Barbee SL, Gergen MF and Sobsey MD, Evaluation of antibiotic resistance bacteria in home kitchens and bathrooms. *Infection Control and Hospital Epidemiology.* 2000; 21, 132.

[87] Aiello AE, Marshall B, Levy SB, la-Latta P and Larson E, Relationship between triclosan and susceptibilities of bacteria isolated from hands in the community. *Antimicrob. Agents Chemother.* 2004; 48, 2973-2979.

[88] Marshall BM, Robleto E, Dumont T, Levy SB The frequency of antibiotic-resistant bacteria in homes differing in their use of surface antibacterial agents *Current Microbiology*, 65, pp. 407-415. Aiello A.E., Marshall B., Levy S.B., Della-Latta P., Lin S.X. and Larson E. (2005) Antibacterial cleaning products and drug resistance. *Emerg Infect Dis.* 2012; 11(10): 1565-1570.

[89] Aiello AE, Marshall B, Levy SB, Della-Latta P, Lin SX, Larson E, Antibacterial cleaning products and drug resistance. *Emerg Infect Dis.* 2005 11(10): 1565-1570.

[90] Cole EC, Addison RM, Rubino JR, Leese KE, Dulaney PD, Newell MS, Wilkins J, Gaber DJ, Wineinger, T. and Criger, D.A., Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. *J. Appl. Microbiol.* 2003; 95, 664-676

[91] Cole EC, Addison RM, Dulaney PD, Leese KE, Madanat HM and Guffey AM, Investigation of antibiotic and antibacterial susceptibility and resistance in *Staphylococcus* form the skin of users and non-users of antibacterial wash products in home environments. *Int. J. Microbiol. Res.* 2011; 3, 90-96.

[92] Marshall BM, Robleto E, Dumont T and Levy SB, The frequency of antibiotic-resistant bacteria in homes differing in their use of surface antibacterial agents *Current Microbiology;* 2012; 65, pp. 407-415.

[93] Rutala WA, Weber DJ, Barbee SL, Gergen, MF and Sobsey MD, Evaluation of antibiotic resistance bacteria in home kitchens and bathrooms. *Infection Control and Hospital Epidemiology.* 2000; 21, 132.

[94] Weber DJ and Rutala WA, Use of germicides in the home and the healthcare setting: is there a relationship between germicide use and antibiotic resistance? *Infection Control and Hospital Epidemiology.* 2006; 27, 1107-1119.

[95] Gilbert P, McBain A and Sreenivasan P, Common therapeutic approaches for the control of oral biofilms: microbiological safety and efficacy. *Clin Microbiol Infect*. 2007; 13 (Suppl. 4): 17–24.

[96] Sreenivasan P and Gaffar A. Antiplaque biocides and bacterial resistance: a review. *J Clin Periodontol*. 2002; 29(11): 965-974.

[97] Cullinan MP, Bird PS, Heng N, West MJM.J. and Seymour GJG.J., No evidence of triclosan-resistant bacteria following long-term use of triclosan-containing toothpaste. *J Periodont Res*. 2014; 49: 220-225.

APPENDIX: The Over-the-Counter OTC Monograph System

The clinical benefit of topical antiseptics in health care settings is well established. In the proposed rule for the consumer antiseptic products, however, the FDA proposes a safety testing program for OTC products similar to those required for new molecular entity (NME) or New Chemical Entity (NCE) review. The active ingredients under the 1994 TFM are not new chemical entities and should not be subjected to requirements that surpass the requirements of a conventional New Drug Application (NDA).

In the FDA's proposal for the consumer TFM, the unsubstantiated justification for additional safety data is stated as "new information regarding the potential risks from systemic absorption and long-term exposure to antiseptic active ingredients" and notes that exposure may be "higher than previously thought."[98] This assertion is not supported by information in the proposed rule for consumer antiseptic products nor in the FDA docket.

The history of the Over-the-Counter (OTC) Drug Review and the OTC Monograph system that it created have shaped the requirements for evidence that demonstrates the safety and effectiveness of OTC monograph drugs. This evidence must prove *general* recognition of safety and effectiveness (GRAS/GRAE), concepts that by their very nature are established by publicly available evidence. The FDA possesses substantial flexibility to implement the GRAS/GRAE standard and make judgments about the adequacy of evidence underlying safety and effectiveness of OTC drugs, including the flexibility to rely on published literature and the proven track-record that comes with substantial human marketing experience.

FDA is in the process of establishing a GRAS/GRAE framework for consumer and healthcare antiseptic drug products (and has been petitioned to establish a framework for food handler antiseptic drug products) in order to be able to finalize an OTC Monograph for Antiseptic Drug Products.

The history of the Over-the-Counter (OTC) Drug Review (or the Review) and the monograph system that it created have shaped the requirements for evidence that demonstrates the safety and effectiveness of OTC drugs. This evidence must prove *general* recognition of safety and effectiveness (GRAS/GRAE) – concepts that by their very nature are established by publicly available evidence. The U.S. Food and Drug Administration (FDA) possesses substantial flexibility to implement the GRAS/GRAE standard and make judgments about the adequacy of evidence underlying safety and effectiveness of OTC drugs, including the flexibility to rely on published literature and, often, on the proven track-record that comes with substantial human marketing experience. FDA then has the power to consider this evidence and any risks associated with the OTC products in proportion to the benefits that the drugs will provide.

The following presentation demonstrates how the monograph system has worked even though the products that it regulates are not supported by precisely the same data and clinical studies as New Drug Applications (NDAs). It first sets forth the history of the OTC Drug Review, the fundamental principles supporting the monograph system, and its successes. It then discusses how FDA has successfully implemented the general recognition standard, by relying

[98] 78 Fed. Reg. at 76445, 76454.

on published studies, substantial human experience, and consideration of the risk benefit ratios associated with OTC drugs.

A. The History and Purposes of the OTC Drug Review

Understanding the history of the OTC Drug Review is critical to understanding how the monograph system works in practice. Prior to 1938, most drugs in the United States were marketed without undergoing review by FDA. In 1938, the Federal Food, Drug and Cosmetic Act (FDCA)[99] required the premarket review for safety of any drug that was a "new drug." A "new drug" was defined as one that was not generally recognized by experts as "safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, *i.e.*, GRAS, or that had not been marketed to a material extent for a material time."[100] Drugs that were on the market in 1938 were permitted to remain on the market under a "grandfather clause" included in the FDCA. In the years following enactment of the FDCA, FDA adopted the practice of declining to review NDAs for products that it did not consider to be new drugs, and thousands of products entered the post-1938 market based upon determinations by FDA or manufacturers that the products were not new drugs.[101]

The 1962 amendments[102] to the FDCA changed the definition of new drug to provide that a drug was new unless it was generally recognized by experts as GRAS/GRAE.[103] A drug that did not meet the GRAS/GRAE requirement (or a drug that met that requirement but that had not been used to a material extent for a material time) was considered a new drug and required an NDA. The 1962 amendments included one exception in the form of a grandfather clause under which drugs that had been lawfully marketed without NDAs prior to enactment of the 1962 amendments could be deemed exempt from the requirement for general recognition of effectiveness, provided that no changes were made in their labeling or formulation.[104] The 1962 amendments further provided that drugs that had entered the market under NDAs between 1938 and 1962 had to be reevaluated for efficacy; and, drugs that claimed to be not new under the 1938 law now had to show a general recognition of efficacy as well as safety (unless they could be shown to comply with the requirements of the 1962 "grandfather clause").

FDA's first step in this reevaluation process was to contract with the National Academy of Sciences/National Research Council to review the efficacy claims of NDA drugs.[105] This review, known as the Drug Efficacy Study Implementation ("DESI"), reviewed approximately 3500 drug products by class or therapeutic category, most of which were prescription drugs

[99] Pub. L. No. 75-717, 52 Stat. 1040 (1938).

[100] FDCA §201(p), 52 Stat. at 1041-42.

[101] *See* Peter Barton Hutt *et al.*, Food And Drug Law: Cases And Materials 579-80 (3d ed. 2007).

[102] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962), *as amended* 21 U.S.C. §§301-399 (2013).

[103] 21 U.S.C. § 321(p).

[104] 21 U.S.C. § 355; Sec. 107(c)(4), Pub. L. 87-781, 76 Stat. 780, 788-89 (1962).

[105] As prescription drugs posed the greater potential for harm and because most prescription drugs are NDA drugs, FDA chose to review NDA drugs first. 37 Fed. Reg. 85, 85-86 (Jan. 5, 1972).

(approximately 420 were OTCs).[106] With this review underway, FDA determined that it was "now appropriate to conduct a similar review of OTC drugs."[107]

The OTC Drug Review was one of the largest regulatory undertakings in the history of FDA. At the time that the Review began, there were anywhere from 100,000 to 300,000 OTC drug products on the market. Many of these products and their active ingredients had enjoyed decades of safe use on the market and had become important, cost-effective elements of "self-medication" that were "essential to the Nation's health care system."[108] FDA concluded that conducting a case-by-case review and/or initiating litigation to remove violative products from the market would take years and consume exceptional amounts of Agency resources, during which time these products would be off the market.[109] Therefore, in May 1972, FDA finalized rules for the OTC Drug Review and adopted the monograph process for determining on the basis of therapeutic categories whether OTC products not covered by NDAs were generally recognized as safe and effective, and therefore, not misbranded.[110]

The monograph process involves several phases. To begin, seventeen panels of expert advisors reviewed data, studies and literature that industry and other stakeholders submitted.[111] The data, studies, and literature that the panels reviewed related to the labeling and active ingredients in various therapeutic categories. On the basis of their review, the panels produced reports that FDA published in the Federal Register, along with a proposed monograph (in the form of an advance notice of proposed rulemaking).

The panel reports contained recommendations to the FDA for use in developing a monograph. There were three possible recommendations the panels could make for ingredients and labeling: (1) GRAS/GRAE status (Category I), (2) non-GRAS/GRAE and, therefore, misbranded (Category II), and (3) insufficient data available to make a classification (Category III). After reviewing comments and data submitted in response to the proposed monograph, FDA published a tentative final monograph (TFM) that sets forth FDA's proposal for allowable claims, dosages, and active ingredients for OTC drugs in the class. As a last step, FDA publishes a final monograph for the class. Drugs marketed in accordance with a final monograph do not require FDA approval of a marketing application.[112]

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[106] See Kenneth C. Baumgartner, *A Historical Examination of the FDA's Review of the Safety and Effectiveness of Over-the-Counter Drugs*, 43 FOOD DRUG COSM. L.J. 463, 466-467 (1988).

[107] 37 Fed. Reg. at 85.

[108] *Id.* at 85.

[109] *Id.* at 86.

[110] 37 Fed. Reg. 9464 (May 11, 1972). Currently codified at 21 C.F.R. § 330.1, et seq. (former § 130.301).

[111] *See, e.g.*, 37 Fed. Reg. 26156 (Dec. 12, 1972) (call for data on sunscreens).

[112] 21 C.F.R. §§330.1, 330.10(a)(9). In addition, many products continue to be marketed under TFMs; FDA has stated it will not, as a general matter, take regulatory action against products covered by pending monographs. See FDA, Compliance Policy Guide, §440.110 app. (2011).

B. The OTC Drug Review generated substantial data to support the monographs

There are now more than 20 final monographs for classes of ingredients that still enjoy a wide margin of safety and are effective as labeled. This is because FDA made GRAS/GRAE determinations on the basis of thorough and deliberate consideration of scientific evidence, data, and stakeholder input. In response to its calls for data published in the Federal Register, FDA received over 20,000 volumes of data upon which the expert panels relied to produce comprehensive reports on the safety and effectiveness of each active ingredient under specified conditions of labeling and marketing.[113] Stakeholders had and have opportunities to present data and studies at each stage of the review.

The monographs allow OTC drug manufacturers to continue to market their safe and effective products with confidence as well as to develop new ones. In addition, the system has resulted in the removal from the market of a number of ingredients that did not meet the GRAS/GRAE standard.[114]

C. FDA's legal authority to review OTC drugs in this manner is now firmly established

FDA's legal authority to review OTC drugs under the GRAS/GRAE standard has withstood various challenges. *First*, the courts have upheld FDA's power to make its own determination as to whether a drug constitutes a "new drug" and requires an NDA. After the 1962 amendments, FDA began the process of taking products off the market that it considered to be unapproved new drugs and withdrawing NDAs of drugs it determined to be ineffective. In a serious of related cases, the Supreme Court concluded that FDA had the power to decide via administrative procedures whether drugs were considered "new drugs" under the FDCA.[115] The Court also held that the determination whether a drug was GRAE under the new drug definition was essentially the same as determining whether "substantial evidence" of efficacy existed to justify approval of an NDA.[116] The Court concluded that a "drug can be generally recognized by experts as effective for intended use within the meaning of the FDCA only when that expert consensus is founded upon substantial evidence."[117]

Second, the OTC Drug Review itself has survived criticism with its foundations intact. For example, in finalizing the rules governing the review FDA noted that it had received comments questioning its authority to establish such rules, particularly its decision to evaluate products by categories. Comments to the Agency argued that category reviews were not legally proper as they subverted the NDA procedures, which call for drug-by-drug review. However, FDA responded that "the regulations…do not state that the OTC drugs reviewed are new drugs which have been approved, but instead provide for monographs which will include those drugs

[113] HUTT, *ET AL.*, at 979; Baumgartner at 474.

[114] For example, hexachlorophene was removed from the OTC marketplace for safety reasons in 1972 (37 Fed. Reg. 20, 160 (Sept. 27, 1972)); tribromsalan in 1975 (40 Fed. Reg. 50,527 (Oct. 30, 1975)).

[115] Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 651-54 (1973); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 626-27 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640, 643-44 (1973).

[116] Bentex Pharm., Inc., 412 U.S. at 652-53; Hynson, Westcott & Dunning, Inc., 412 U.S. at 689-90.

[117] 412 U.S. at 632.

that do not require an NDA."[118] FDA further stated "[n]othing in the act [FDCA] prohibits the use of the therapeutic category approach to defining those OTC drugs that are generally recognized as safe and effective and not misbranded."[119] Throughout the 1970s, a number of legal challenges questioned FDA's approach to the OTC Drug Review,[120] but none has damaged the basic principles of the monograph system set forth above.

D. FDA has implemented the GRAS/GRAE standard in a flexible and effective manner

Neither the FDCA nor the regulations for NDAs or the OTC Drug Review articulate a specific recipe for determining safety.[121] The instructions provided to the expert panels in the OTC Drug Review emphasized this fact. In the words of FDA's Chief Counsel at the time, "it's quite clear that [FDA] could not write a definition [of safety] that would be overly helpful to [the panels]. In the last analysis, the judgment on safety is a judgment. It is a judgment of experts who are qualified to analyze toxicological and pharmacological data and to balance the benefit and risk and make judgments of this type."[122] The test of safety, therefore, is one that is consistently left to FDA's discretion and common sense.

While the standard for safety for a monograph product may be no different from that for an NDA product in a legal sense,[123] acceptable evidence of safety will necessarily be context-dependent. Three points are significant. *First*, the concept of general recognition on its face requires that the information underlying that determination be publicly available; otherwise, it would be impossible to determine general recognition. The OTC Drug Review expressly recognized that the best evidence of safety and effectiveness would be "published studies,"[124] and the expert review panels relied heavily on reports published in professional journals in their review of different therapeutic categories.[125] However, those published studies are often likely to be very different from, for example, the detailed reports of toxicological studies that typically accompany NDAs.

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[118] 37 Fed. Reg. at 9464-9465.

[119] *Id.*

[120] *See, e.g.,* Cutler v. Kennedy, 475 F. Supp. 838, 856-57 (1979) (concluding that an FDA rule permitting continued marketing of Category III ingredients after final monograph pending studies was unlawful).

[121] *See* 21 U.S.C. § 355(d)(1) (safety is established by "all methods reasonably applicable to show whether a drug is safe"); 21 C.F.R. § 330.10(a)(4)(i); *see also* 37 Fed. Reg. at 9468 (noting FDA removed the word "all" to modify methods reasonably applicable to prove safety from the final rules governing the OTC Drug Review to "avoid the unwarranted interpretation that every conceivable test is required.").

[122] Peter B. Hutt, *Remarks to FDA's Panel for Review of Over-the-Counter Antimicrobial II (Topical Antibiotic) Products* at 9 (July 26, 1974).

[123] *See* Hynson, Westcott & Dunning, Inc., 412 U.S. at 629-30.

[124] 21 C.F.R. § 330.10(a)(4)(i)-(ii).

[125] *See, e.g.,* 43 Fed. Reg. 64628, 64628-36 (Aug. 4, 1978) (panel report relying on published journal articles in support of proposed skin protectant monograph); 42 Fed. Reg. 63556, 63561-62 (Dec. 16, 1978) (panel report citing, in one place, 52 published reports in support of conclusions related to the general safety and effectiveness of topical otic drugs).

Even in the NDA context, however, FDA has accepted publicly available literature to support determinations of safety and effectiveness. Courts have expressly ratified this policy, referred to as the "Paper NDA,"[126] as in accordance with FDA's mandate under the FDCA.[127] In subsequent statements related to the Paper NDA policy, FDA emphasized its long commitment to basing safety and effectiveness decisions on published literature:

> [T]he [A]gency may accept published reports as the sole basis for establishing safety and effectiveness (except for bioavailability data as required). Reports in scientific literature are often subject to peer review prior to publication, and the investigations reported are often repeated by other engaged in similar research. The [A]gency's recognition of the reliability of a group of independently published reports of adequate and well-controlled studies, all of which reach consistent conclusions relating to the safety and effectiveness of a drug, has influenced a variety of [A]gency decisions, including some concerning labeling changes that add new indications and new warnings for approved drugs.[128]

Since that time, FDA has continued to accept published reports to support determinations of safety and effectiveness in other contexts.[129]

Second, both the OTC Drug Review, and the Time and Extent Application (TEA) process that followed later, recognized the value of extensive and continued human use in determining safety. The value placed on human experience with a drug with few associated serious adverse events has roots in other areas of policy for FDA. This includes a policy that some regularly consumed foods may be considered generally recognized as safe based on common use.[130]

FDA developed the TEA process to permit extensive foreign marketing experience with over-the-counter drugs to support determinations of safety and effectiveness in the U.S.[131] This process should permit FDA to conserve resources and not engage in an unnecessarily extensive review of ingredients that enjoy a long-standing safety record abroad.

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[126] 46 Fed. Reg. 27369, 27369-70 (May 19, 1981).

[127] *See, e.g.*, Upjohn Manufacturing Co. v Schweiker, *et al.*, 681 F.2d 480 (6th Cir. 1982); Burroughs Welcome v. Schweiker, *et al.*, 649 F.2d 221, 225-26 (4th Cir. 1981).

[128] FDA Response to Citizen Petition 81P-0259/CP (Dec. 2, 1982).

[129] *See, e.g.*, 68 Fed. Reg. 5646, 5647 (Feb. 4, 2003) ("We have reviewed the published literature and have determined that 500–mg prussian blue capsules, when produced under conditions specified in an approved NDA, can be found to be safe and effective for the treatment of patients with known or suspected internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium."); *see also* 62 Fed. Reg. 8610, 8610-11 (Feb. 25, 1997) (relying on experience abroad for safety and published articles for effectiveness for certain oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel).

[130] *See* 21 U.S.C. § 321(s) (permitting use of food generally recognized as safe prior to January 1, 1958 solely based on "common use").

[131] *See* 67 Fed. Reg. 3060 (Jan. 23, 2002); *see also* Fmail Herb, Inc. v. Heckler, 715 F.2d 1385, 1390-91 (9th Cir. 1983).

The regulations governing the OTC Drug Review also acknowledge the value of human experience in that they define safety as a "low incidence of adverse events or significant side effects under adequate directions of use as well as the low potential for harm…under conditions of widespread availability."[132] And, the regulations require proof of safety that includes "results of significant human experience during marketing."[133] This standard has worked well in practice. Many of the ingredients that were part of and confirmed as GRAS/E under the OTC Drug Review had been on the market in the U.S. for decades, and have proven both before and after the Review to be both safe and effective.[134]

Third, as with an NDA, FDA will also evaluate safety risks in light of the benefits of OTC products and ingredients that it reviews. This is a requirement in the regulations governing the monograph system, [135] and it has otherwise been a long-standing practice of FDA.[136] As Center for Drug Evaluation and Research Director Janet Woodcock recently stated in a Congressional hearing:

> FDA has considerable flexibility in applying the safety and efficacy standards, and we basically use a sliding scale. So for a headache, a drug has to be pretty safe because no one wants to risk their life to cure their headache, right? On the other hand, for serious and life threatening diseases where there isn't any alternative, there is a lot of tolerance of risk, and there is also greater tolerance of uncertainty about the effects…[137]

Therefore, when the benefits are significant, lifesaving benefits, such as the prevention of serious diseases, FDA has the flexibility to tolerate potentially greater safety risks. Prior experience also demonstrates that FDA takes more practical considerations into account outside of the data when evaluating the risk-benefit ratio, such as whether certain side effects may be managed outside of the clinical trial context and post-marketing experience with other similar drugs.[138]

Finally, to the extent not already stated, the considerations above apply with similar force to proving general recognition of effectiveness under the monograph system. FDA has stated in

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[132] 21 C.F.R. § 330.10(a)(4)(i).

[133] *Id.*

[134] Peter Hutt, *Remarks to FDA's Panel for Review of Over-the-Counter Antimicrobial II (Topical Antibiotic) Products* at 10.

[135] 21 C.F.R. § 330.10(a)(4)(iii).

[136] 78 Fed. Reg. 76444, 76444-45 (Dec. 17, 2013) (acknowledging risk-benefit ratio in determining GRAS/E status); *see also* Richard Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 9 (1973).

[137] *FDA Checkup: Drug Development and Manufacturing Challenges, Hearing Before the H. Subcomm. on Energy Policy and Health Care Entitlements of the Comm. on Oversight and Government Reform*, 113th Cong. 1 (2013) (statement of Dr. Janet Woodcock, Dir. FDA Center for Drug Evaluation and Research).

[138] *FDA Often Looks Outside the Applications, Review Documents Show*, PINK SHEET (Mar. 17, 2014) (citing examples).

various contexts that published reports of adequate and well-controlled clinical studies can be sufficient to support a conclusion of substantial evidence of effectiveness.[139] The OTC Drug Review also recognized that in some instances a century of human experience with an ingredient would obviate the need for adequate and well-controlled studies to prove effectiveness. In instructing an expert panel during the Review, FDA's chief counsel noted "we recognize that there are some over-the-counter medications, in particular, where it simply would not make sense to go back on a product that's been on the market for a hundred years and is absolutely recognized by everyone as effective – and run an adequate and well-controlled clinical study."[140]

[139] 21 C.F.R. § 330.10(a)(4)(ii). *See also* 68 Fed. Reg. at 5647; 62 Fed. Reg. at 8610-11 (relying on published articles for effectiveness for certain oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel).

[140] Peter Hutt, *Remarks to FDA's Panel for Review of Over-the-Counter Antimicrobial II (Topical Antibiotic) Products* at 10.